International Journal of Infectious Diseases 134 (2023) 23–30

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Overall effect of a campaign with measles vaccine on the composite outcome mortality or hospital admission: A cluster-randomized trial among children aged 9-59 months in rural Guinea-Bissau

Anshu Varma[1,2], Sanne M. Thysen[1,2], Justiniano S.D. Martins[1], Line M. Nanque[1,2], Aksel K.G. Jensen[3], Ane B. Fisker[1,2,*]

[1] Bandim Health Project, INDEPTH Network, Bissau, Guinea-Bissau
[2] OPEN, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark
[3] Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 14 August 2022
Revised 6 May 2023
Accepted 9 May 2023

Keywords:
Measles vaccine
Non-specific (heterologous) effects
Death
Hospital admission
Children
Guinea-Bissa

ABSTRACT

Objectives: Campaigns with measles vaccine (C-MV) are conducted to eradicate measles, but prior studies indicate that MV reduces non-measles mortality and hospital admissions too. We hypothesized that C-MV reduces death/hospital admission by 30%.

Methods: Between 2016-2019, we conducted a non-blinded cluster-randomized trial randomizing village clusters in rural Guinea-Bissau to a C-MV targeting children aged 9-59 months. In Cox proportional hazards models, we assessed the effect of C-MV, obtaining hazard ratios (HR) for the composite outcome (death/hospital admission). We also examined potential effect modifiers.

Results: Among 18,411 children (9636 in 111 intervention clusters/8775 in 110 control clusters), 379 events occurred (208 intervention/171 control) during a median follow-up period of 22 months. C-MV did not reduce the composite outcome (HR 1.12, 95% confidence interval 0.88-1.41). Mortality among enrolled children (5.3 intervention and 4.6 control, per 1000 person-years) was approximately half the pre-trial mortality rate (11.1 intervention and 8.9 control, per 1000 person-years). Neither planned nor explorative analyses of potential effect modifiers explained the contrasting results to prior studies.

Conclusion: C-MV did not reduce overall mortality or hospital admission. This might be explained by changes in disease patterns, baseline differences in health status, and/or modifying effects of other campaigns during follow-up.

Introduction

In the past decades, the world has implemented numerous campaigns with measles vaccine (C-MV) to control and ultimately eradicate measles [1]. During the same decades, overall child mortality has decreased tremendously [2]. Meanwhile, accumulating evidence suggests that MV also prevents infections unrelated to measles [3]. Such potential beneficial non-specific-effects (NSEs) of MV [3] have been examined in an epidemiological review commissioned by the World Health Organization [4]. The review concluded that the evidence is consistent with beneficial NSEs of MV [4].

Observational studies have suggested substantial beneficial NSEs of C-MV in children [5–9]: MV was introduced as a campaign to 600 children in Guinea-Bissau in 1979. Following the campaign overall mortality fell by more than 50%, a decline which could not be fully explained by measles prevention [8]. Similar declines were observed during the introduction of MV as a campaign across several settings in Africa [9] and Bangladesh [7]. More recently, in two studies from Guinea-Bissau, the potential beneficial NSEs of C-MV have been evaluated after the rollout of a routine vaccination program with MV offered at 9 months of age [5,6]. Among 8000 children, most of whom had already received routine MV, overall mortality after vs before a national C-MV in 2006 was 20% (4-34%) lower. The effect remained largely unchanged after censoring measles deaths [6]. Among 6639 children, most of whom had already received routine MV, overall mortality after a national C-MV in 2012 was 72% (23-90%) lower among participants than non-participants. Measles caused none of the deaths [5].

We think that C-MV may have contributed efficiently to the decrease in overall child mortality beyond our common understanding. However, to our knowledge, no randomized trial has assessed

* Corresponding author. Tel: +45 65503740.
E-mail address: afisker@health.sdu.dk (A.B. Fisker).

https://doi.org/10.1016/j.ijid.2023.05.011

the potential beneficial NSEs of MV provided in a campaign after MV has been offered in a routine vaccination program. Thus, to assess the effects of C-MVs before measles is eradicated, we conducted a cluster-randomized trial: Real-life Effects of a CAMPaign with Measles Vaccine (RECAMP-MV) [10]. In RECAMP-MV, we assessed whether a C-MV reduces the risk of non-accidental mortality or non-accidental hospital admissions by 30%, among children aged 9-59 months from rural Guinea-Bissau [10], a setting with limited measles [11,12] and regular national C-MVs [13].

Methods

Study design

The protocol of RECAMP-MV is published elsewhere [10]. Briefly, RECAMP-MV was a cluster-randomized trial [10] using the platform of Bandim Health Project's rural health and demographic surveillance system (HDSS) in Guinea-Bissau which has existed since 1990 [14].

Participants

The rural HDSS monitors roughly 22,000 children aged 0-59 months in 10 health regions covering 222 village clusters [14]. Every 6 months, field teams of assistants and nurses visit the village clusters where field assistants conduct structured interviews with mothers to register pregnancies and births [14]. For children under surveillance, field assistants register routine vaccinations (Appendix p 2), participation in other health interventions (Appendix p 3), and hospital admissions [14]. Children are followed until migration, death, or 5 years of age [14]. Furthermore, immediately after registration of a death or a hospital admission, field assistants conduct a short interview to assess the cause of either event [14] and subsequently, specially trained field assistants conduct verbal autopsies [15].

Using this platform for RECAMP-MV, we enrolled children aged 9-59 months [10], as this is the age group targeted in Guinea-Bissau's regular national C-MVs [16]. We followed the enrolled children as per the rural HDSS' routines [14] but extended the follow-up beyond 5 years to increase power.

Randomization and masking

We randomized HDSS village clusters stratified by region (11 strata corresponding to the original HDSS sampling frame) and pre-trial vaccination coverage (high/low) [10]. Children in half of the village clusters received C-MV and a health check (intervention group) and children in the other half received only a health check (control group) [10]. RECAMP-MV was a non-blinded trial. Details on RECAMP-MV's randomization procedure and justification for non-blinding are described elsewhere [10].

Procedures

We initiated enrollment visits to village clusters in November 2016. At these visits, field assistants visited all households and referred potentially eligible children aged 9-59 months to the field nurse who performed the health checks at an enrollment post set up in the village. Due to the presence of other children and mothers at the enrollment post, the mother would frequently know the trial arm before enrollment. A child was offered enrollment if it was not: acutely ill, with high fever (axillary temperature $>39°C$), severely malnourished (mid-upper-arm circumference <110 mm), with a history of allergic reactions to prior vaccination, or enrolled in a concurrent trial utilizing the same cluster-randomized set up and focusing on the NSEs of an oral polio vaccine (OPV) campaign in children aged 0-8 months [10]. Field nurses administered a standard 0.5 ml MV dose (Edmonston-Zagreb strain from Serum Institute of India) to children enrolled in the intervention group. The last enrollment visits were conducted in January 2019.

We followed the enrolled children through the rural HDSS from November 2016 to May 2019. On May 03, 2019, a national C-MV was implemented by the Ministry of Health. To ensure that we had information on the enrolled children's death and hospital admission status until the national C-MV, we visited the enrolled children once after the national C-MV, finalizing these visits in December 2019 (Appendix p 3).

The study protocol was approved by Guinea-Bissau's national ethics committee (Comité Nacional de Ética na Saúde: CNES/2016/020) and Denmark's national ethics committee provided a consultative approval (Den Nationale Videnskabsetiske Komité: 1606756). We enrolled children whose mothers/guardians provided written informed consent [10]. A data monitoring committee followed RECAMP-MV. We registered RECAMP-MV at clinicaltrials.gov (NCT03460002).

Outcomes

In prior studies [3], the overall effect of MV has mostly been measured on mortality. Nevertheless, in studies assessing the effect of MV on hospital admission, a similar overall effect has been observed [17,18]. Thus, given that child mortality has decreased tremendously in the last decades [19], we used a composite outcome of death or hospital admissions to measure the overall effect of MV.

Our primary outcome was a composite outcome of a non-accidental death or a non-accidental hospital admission [10]. Hospital admissions were defined as a first non-fatal hospital admission with an overnight stay thus giving equal weight to deaths and hospital admissions. Onwards, we refer to our primary outcome as 'mortality/hospital admission' or 'death/hospital admission', implicitly understood as a composite outcome, due to any cause except an accident and reported during a household visit. We estimated that enrolling 18,000 children would give us 80% power to detect a 30% reduction in mortality/hospital admission (17 events per 1000 person-years in the control group, harmonic mean observation time per cluster: 84 years) [10]. In Appendix p 4, we have provided the interview questions used to retrieve information on the primary outcome.

Secondary outcomes for all the enrolled children were mortality, hospital admission, and cause-specific mortality/hospital admission (due to malaria infection, gastrointestinal infection, or respiratory infection) [10]. Secondary outcomes assessed for a subgroup of the enrolled children were episodes of non-accidental outpatient consultation and illness within 3 months after enrollment [10] and the assessment of these short-term adverse events of C-MV is reported elsewhere [20].

Statistical analyses

Children contributed observation time from the date of enrollment until their reported date of first event or censoring due to migration, death caused by accident, or trial end (national C-MV on May 03, 2019). Except for the analysis of the secondary outcome of hospital admission, children did not re-enter the analysis after an event. We used Cox proportional hazards models with age as the underlying timescale to compare event rates in the intervention group with the control group, based on individual-level data [10]. We estimated hazard ratios (HR) with 95% confidence intervals (CI) adjusted for the variables used for the stratified cluster randomization (region and pre-enrollment vaccination coverage) and sex [10].

We used robust standard errors to account for intra-cluster correlation. We assessed the proportional hazards assumption with global tests based on Schoenfeld residuals and log-log plots.

Our main conclusion was based on a per-protocol analysis of C-MV's overall effect on mortality/hospital admission [10]. We ignored any hospital admission due to an accident but censored the admission period. Unless otherwise specified, we used the same statistical approach to conduct our planned analyses of [10]:

- secondary outcomes (mortality, hospital admission, cause-specific mortality/hospital admission).
- potential effect modifiers previously shown to be associated with the magnitude of MV's beneficial NSEs. We used Wald tests to compare effects across the strata of each potential modifier: sex [18], season of enrollment [18], prior routine MV [21], and eligibility for national campaigns with OPV [22] and vitamin A supplementation (VAS) [23]. Two types of national campaigns were implemented during follow-up (OPV+VAS and VAS only) and we analyzed the three possible combinations of these interventions: (i) OPV+VAS, (ii) VAS (±OPV), and (iii) VAS only. The observation time for the individual child was split at the first date of eligibility for a national campaign after enrollment, and we compared the HRs for C-MV before and after the national campaign. No other national campaign was conducted during the trial.
- mortality/hospital admission according to two intention-to-treat (ITT) analyses: (i) a conventional ITT analysis where we added children to the main analysis, who were present in the village on the day they were first potentially eligible to be enrolled but were not enrolled (due to illness, no guardian present, refusal/busy, or erroneous assignment during enrollment). (ii) an extended ITT analysis where we added children to the conventional ITT analysis, who could have been enrolled, had they been present (MV may also affect the health of other children in the community by reducing the overall infectious pressure, and thus affect children who were not at home on the enrollment day).

The same statistical approach was used to conduct explorative analyses of C-MVs effect. Secondary and explorative analyses were conducted to assess patterns and were not corrected for multiple testing. Further details on the methods of our explorative analyses are described in Appendix p 5. For all statistical analyses, we used STATA 16.

Role of the funding source

The funding agencies of RECAMP-MV had no role in the trial design, data collection, data analysis, data interpretation, or dissemination.

Results

We enrolled 18,411 children (9636 intervention/8775 control) living in 221 village clusters (111 intervention/110 control) over a 2-year period (November 16, 2016, and January 31, 2019) (Figure 1) with a median age of 33 months (Table 1). The baseline characteristics were balanced between the groups (Table 1 and Appendix p 6). However, 2 years before trial implementation, the overall mortality in the age group 9-59 months tended to be higher in the intervention group (11.1/1000 person-years) than in the control group (8.9/1000 person-years) (HR 1.22, 95% CI 0.94-1.58) (Table 1).

We enrolled 88% of children (88% intervention/88% control) who were residents in the village clusters when visited between the age of 9-59 months and not followed in another Bandim Health Project trial. No child was lost to follow-up as children who migrated after enrollment contributed information until the date of migration. We obtained information on the outcome status during the full planned follow-up period for 92% of the enrolled children (92% intervention/91% control) (Figure 1). We followed the children for a median of 22 months (22 intervention/22 control) (Table 1). We censored 12 deaths due to accidents (five intervention/seven control) and ignored six hospital admissions due to accidents (two intervention/four control). No death/hospital admission was reported as measles-related (Appendix p 7). For the main analysis, we included 29,405 person-years at risk (15,423 intervention/13,982 control) resulting in 379 deaths/hospital admissions (208 intervention/171 control), generating a composite outcome rate of 12.8 deaths/hospital admissions per 1000 person-years at risk (13.5 intervention/12.2 control) (Table 2).

C-MV did not reduce the risk of mortality/hospital admission (HR 1.12, 95% CI 0.88-1.41) (Table 2). We found no indication that the proportional hazards assumption was violated. For separated outcomes, this overall negative health effect tended to be stronger for hospital admission (HR 1.20, 95% CI 0.89-1.61) (Appendix p 8-9) than for mortality (HR 1.07, 95% CI 0.79-1.46) (Appendix p 10-11); the number of children who died after being admitted to hospital was twice as high in the intervention group (38/165) as in the control group (14/122) (Figure 1) (relative risk 2.05, 95% CI 1.15-3.67) (Appendix p 12). Twelve percent of hospital admissions and 6% of deaths were due to respiratory infections (Appendix p 7); the point estimate for mortality/hospital admission due to respiratory infection indicated a potential reduction but the CI was wide (HR 0.82, 95% CI 0.42-1.63) (Table 2). There was no indication of a reduction in the other main causes, malaria infection, and gastrointestinal infection in the intervention group (Table 2).

None of the potential effect modifiers (sex, season at enrollment, prior routine MV, and campaigns with OPV and VAS before enrollment or during follow-up) showed statistically significant interactions (Table 3). The ITT analyses gave similar estimates ($HR_{conventional}$ 1.14, 95% CI 0.91-1.44 and $HR_{extended}$ 1.14, 95% CI 0.92-1.39) (Appendix p 13) to our per-protocol analysis (Table 2).

To understand why C-MV did not reduce mortality/hospital admission, we explored whether the effect of C-MV varied by sex. Across our planned effect modifiers we found no sex-differential effects of C-MV by prior routine MV, season, or campaigns with OPV and VAS before enrollment (Appendix p 14-15). However, for campaigns with OPV and VAS during follow-up, our pre-planned analyses showed that C-MV's effect tended to be negative after exposure to any of the three campaign combinations (OPV+VAS, VAS ± OPV, VAS only) (Table 3).

For the two mutually exclusive combinations (OPV+VAS and VAS only), the differential effect was similar for OPV+VAS (HR_{before} 1.01, 95% CI 0.72-1.42; HR_{after} 1.24, 95% CI 0.92-1.68, $P = 0.35$) and for VAS only (HR_{before} 1.04, 95% CI 0.77-1.42; HR_{after} 1.20, 95% CI 0.84-1.73, $P = 0.56$) (Table 3). However, as previous trials have suggested that OPV may interfere with MV's potential beneficial NSE [22,24–27], we focused the reporting here on the sex-differential effects of C-MV before/after OPV+VAS campaigns during follow-up. This revealed that the effect of C-MV before/after OPV+VAS campaigns during follow-up was similar for boys (HR_{before} 1.12, 95% CI 0.72-1.75; HR_{after} 1.06, 95% CI 0.72-1.57) but tended to be different for girls (HR_{before} 0.86, 95% CI 0.53-1.37; HR_{after} 1.52, 95% CI 1.02-2.27) ($P = 0.11$ for C-MV*OPV+VAS*sex; $P = 0.06$ for C-MV*OPV+VAS in girls; $P = 0.84$ for C-MV*OPV+VAS in boys) (Appendix p 14-15). The sex-differential pattern before/after OPV+VAS campaigns tended to be stronger for hospital admissions (Appendix p 8-9) than for mortality (Appendix p 10-11).

We also conducted explorative analyses investigating whether the overall effect of C-MV on mortality/hospital admission varied by newer routine vaccinations (Appendix p 16-17), demographics (Appendix p 18-19), length of follow-up (Appendix p 20-21), calendar time period (Appendix p 22), pre-trial mortality (Appendix

Table 1
Baseline characteristics of children per group assignment. Percentage (n). Median (interquartile range). Mean (standard deviation).

N = 18411[a]	C-MV[b]		No C-MV	
	52.3	(9636)	47.7	(8775)
Socio-demographics				
Male	51	(4908)	51	(4483)
Age, months, median (IQR)	33	(20-46)	33	(21-46)
Health region				
Oio	14	(1381)	16	(1396)
Biombo	11	(1102)	11	(927)
Gabu	11	(1107)	10	(880)
Cacheu	9	(866)	6	(489)
Bafata	9	(823)	13	(1112)
Quinara	8	(765)	9	(774)
Tombali	7	(721)	9	(828)
Bubaque	2	(235)	2	(201)
Bolama	1	(133)	2	(145)
Sao Domingos	9	(857)	8	(723)
Bafata new[c]	17	(1646)	15	(1300)
Ethnicity				
Balanta	24	(2289)	25	(2208)
Fula	31	(2974)	26	(2282)
Manjaco/Mancanha	6	(616)	5	(397)
Pepel	9	(888)	9	(816)
Mandinga	15	(1464)	20	(1758)
Other	14	(1308)	14	(1218)
Household characteristics				
Zinc/metal roof	70	(6698)	66	(5770)
Radio	81	(7821)	82	(7238)
Outdoor toilet	80	(7711)	81	(7108)
Phone (own/house)	53	(5086)	50	(4431)
Mother's age at birth of child, yrs, mean (SD)	27	(7.2)	27	(7.2)
Mother attended school	40	(3878)	41	(3629)
Child lives with mother	97	(9316)	97	(8508)
Health status on enrollment day				
Weight, kg, mean (SD)	11.6	(2.6)	11.7	(2.6)
Weight for age, z-score, mean (SD)	-1.2	(1.1)	-1.2	(1)
MUAC, mm, mean (SD)	147.6	(11.9)	147.3	(11.9)
MUAC for age, z-score, mean (SD)	-0.6	(0.9)	-0.6	(0.9)
No medicine intake	97	(9392)	98	(8583)
Vaccination status among children with vaccination card seen prior enrollment				
Vaccination card seen	76	(7277)	74	(6458)
Already administered routine vaccinations				
BCG	93	(6733)	93	(5986)
PENTA 3rd (+OPV)	90	(6557)	90	(5835)
Pneumococcal conjugate 3rd	43	(3094)	42	(2726)
Rotavirus 2nd	29	(2102)	29	(1892)
Yellow fever	73	(5295)	72	(4669)
MV	81	(5872)	80	(5192)
Inactivated polio	14	(1038)	14	(895)
Most recent vaccination before enrolment[d]				
MV[e]	40	(3881)	40	(3529)
PENTA+MV[f]	5	(498)	5	(448)
PENTA[g]	13	(1237)	13	(1103)
Eligibility to other vaccination campaigns				
Prior enrollment				
Any OPV (± VAS[h]) campaign (since 2012)	85	(8228)	85	(7497)
Any VAS[h] (± OPV) campaign (since 2012)	98	(9480)	98	(8593)
During follow-up				
Any OPV+VAS[h] campaign[i]	74	(7166)	76	(6630)
Any VAS[h] (± OPV) campaign[j]	76	(7315)	77	(6759)
VAS[h] only campaign[k]	48	(4672)	45	(3973)
Timing				
Enrolled during rainy season (Jun-Nov)	47	(4548)	51	(4434)
Enrolled during the first village visit	76	(6511)	74	(7347)
Follow-up time, months, median (IQR)	22	(11-25)	22	(11-25)
Clusters				
Children per cluster, median (IQR)	101	(78-123)	85	(68-133)
Number of clusters visited[l]	50	(111)	50	(110)
Pre-trial mortality rate/1000 PYRS[m]	11.1	NA	8.9	NA

BCG, Bacille Calmette Guerin vaccine; C-MV, Campaign with measles vaccine; HR, hazard ratio; IQR, interquartile range; MUAC, mid-upper-arm circumference; MV, measles vaccine; NA, not applicable; OPV, oral polio vaccine; PENTA, diphtheria, tetanus, pertussis, hepatitis type b, and haemophilus influenza type b vaccine; PYRS, person-years; VAS, vitamin A supplementation.

[a] Number of children with missing values for each variable is provided in appendix p 7.

[b] Data is presented with % (n) unless otherwise stated.

[c] We added clusters from another part of Bafata after approval of a protocol amendment on a sample size increase.

[d] 2932 children (1611 intervention/1321 control) with other combinations of their most recent vaccination were not included.

[e] MV as most recent vaccination; co-scheduled yellow fever could have been given, but not BCG, OPV, PENTA, rotavirus, pneumococcal conjugate, and inactivated polio.

[f] PENTA+MV as most recent vaccination; other vaccines co-scheduled with PENTA or MV could have been given (OPV, rotavirus, yellow fever, pneumococcal conjugate, inactivated polio) but not BCG.

[g] PENTA as most recent vaccination; other vaccines co-scheduled with PENTA could have been given (OPV, rotavirus, pneumococcal conjugate, inactivated polio) but not BCG, MV, and yellow fever.

[h] VAS campaigns were co-administered with mebendazole to children >12 months.

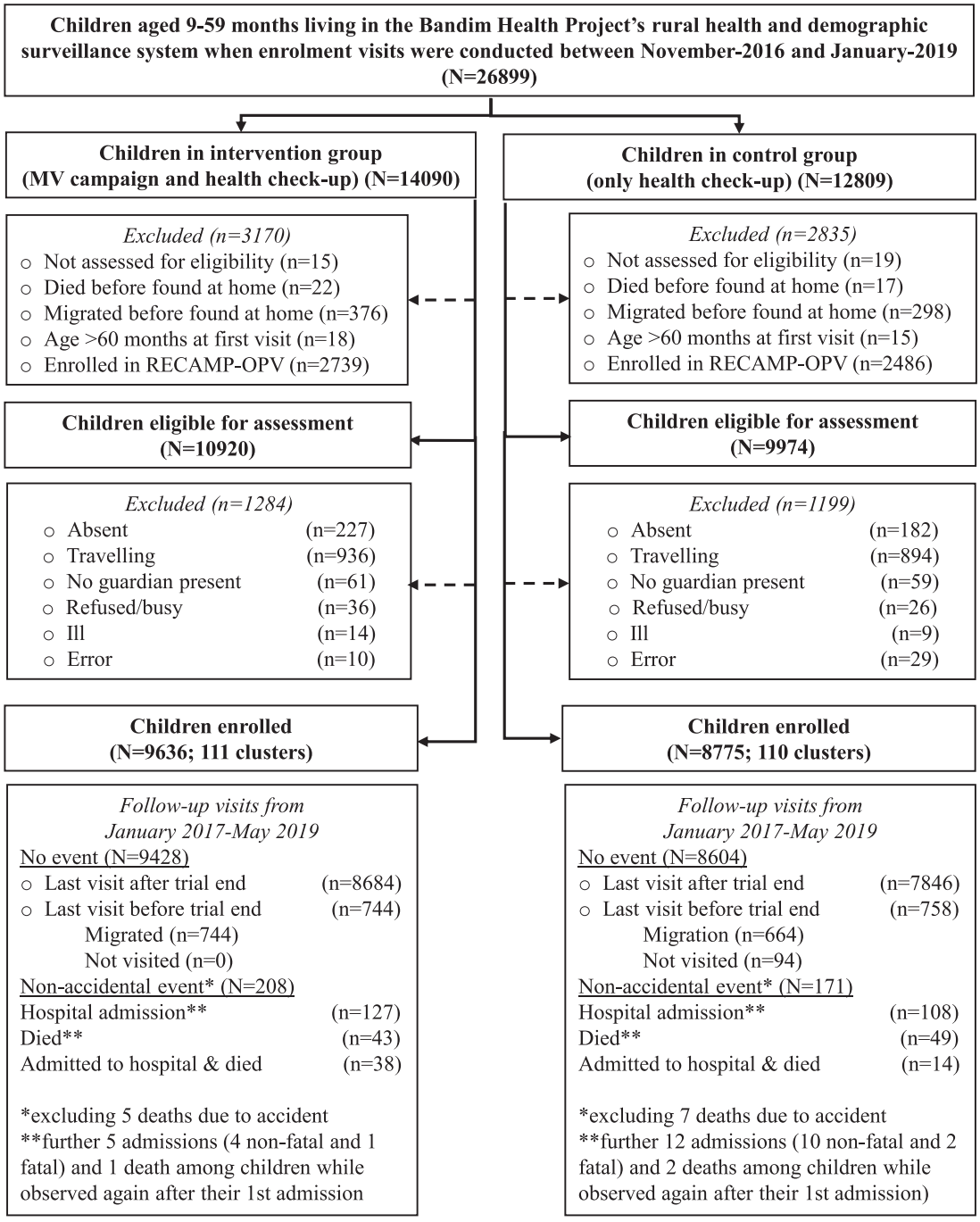
[i] Children were under follow-up at the time of OPV+VAS campaigns in 2017 (November) or 2018 (April).

[j] Children were under follow-up at the time of VAS (± OPV) campaigns in 2017 (January, June, November) or 2018 (April).

[k] Children were under follow-up at the time of VAS-only campaigns in 2017 (January, June).

[l] One cluster in the control group of Bafata was not visited due to inaccessibility.

[m] Pre-trial mortality was assessed in children aged 9-59 months 2 years before starting enrollment. HR for children living in intervention clusters (203 deaths in 18,295 PYRS) vs children living in control clusters (152 deaths in 16,999 PYRS) was 1.22 (95% confidence interval 0.94-1.58).



Abbreviations: MV=measles vaccine. OPV=oral polio vaccine

Figure 1. Flow of children from eligibility to analysis. MV, measles vaccine; OPV, oral polio vaccine; RECAMP, Real-life Effects of a CAMPaign.

p 23), or healthcare-seeking behavior (Appendix p 24). However, we identified no explanation for the lack of a beneficial effect of C-MV.

Discussion

In this cluster-randomized trial, we did not find beneficial NSEs of a C-MV. This is a surprising finding given that previous studies, both individually randomized and observational, have indicated beneficial NSEs of MV [3,5–9]. While explorative analyses indicated that C-MV may reduce mortality/hospital admission before OPV+VAS campaigns during follow-up, the magnitude of this reduction, which was only observed in girls (14%), was substantially lower than what we had hypothesized (30%) [10].

The strengths of RECAMP-MV are its sample size, cluster randomization, stratified randomization by health region and pre-trial vaccination coverage, and no loss to follow-up. However, RECAMP-MV also has limitations. First, the fact that we observed pre-trial mortality that was 22% higher in the intervention group than in the control group (Table 1). This is likely to have reduced our chance of observing a potential beneficial effect of C-MV. However, adjusting for or stratifying by the pre-trial mortality quartiles (Appendix p 23) did not affect conclusions. Second, RECAMP-MV was a non-blinded trial. Thus, we cannot rule out differential self-

Table 2
Effect of C-MV on non-accidental mortality/hospital admission. Planned analyses. Cox proportional hazards model.

Number of children = 18,411	C-MV (%, n)		No C-MV (%, n)		Hazard ratio[a]	(95% confidence interval)
	52.3 Rate	(9636) (Events/1000 PYRS)	47.7 Rate	(8775) (Events/1000 PYRS)		
Mortality/hospital admission[b]	13.5	(208/15423)	12.2	(171/13982)	1.12	(0.88-1.41)
Mortality/hospital admission due to malaria infection[c]	4.3	(66/15423)	4.0	(56/13982)	1.09	(0.74-1.61)
Mortality/hospital admission due to gastrointestinal infection[c]	3.9	(60/15423)	3.3	(46/13982)	1.13	(0.77-1.66)
Mortality/hospital admission due to respiratory infection[c]	1.2	(18/15423)	1.3	(18/13982)	0.82	(0.42-1.63)

C-MV, Campaign with measles vaccine; PYRS, person-years at risk.
[a] Adjusted for variables used for the stratified randomization (health region and pre-enrollment vaccination coverage), and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption fulfilled unless otherwise stated.
[b] We censored 12 deaths due to accident (five intervention/seven control) and the admission period of six hospital admissions due to accidents (two intervention/four control). None of the deaths or hospital admissions were due to measles infection. See appendix p. 8 for details on causes.
[c] Observation time of children with deaths/hospital admissions due to other causes than the one in question was censored. The cause categories were not mutually exclusive.

Table 3
Potential effect modifiers of C-MV on the risk of non-accidental mortality/hospital admission. Planned analyses. Cox proportional hazards model.

Number of children = 18,411	C-MV (%, n)		No C-MV (%, n)		HR[a]	(95% confidence interval)	*P*-value[b]
	52.3 Rate	(9636) (Events/1000 PYRS)	47.7 Rate	(8775) (Events/1000 PYRS)			
Sex							0.73
Boys	14.8	(118/7947)	13.6	(99/7255)	1.09	(0.81-1.47)	
Girls	12.0	(90/7476)	10.7	(72/6728)	1.17	(0.85-1.59)	
Season							0.56
Dry	13.0	(126/9685)	11.4	(92/8085)	1.19	(0.85-1.64)	
Rainy	14.3	(82/5738)	13.4	(79/5898)	1.02	(0.72-1.46)	
Prior routine MV among children with seen vaccination card							0.62
Yes	12.9	(124/9625)	10.9	(93/8528)	1.17	(0.87-1.57)	
No	17.0	(37/2176)	14.0	(26/1863)	1.34	(0.82-2.17)	
Before enrollment in any OPV (± VAS[c]) campaign (since 2012)							0.69
Yes	11.8	(152/12851)	10.7	(125/11650)	1.09	(0.84-1.43)	
No	21.8	(56/2572)	19.7	(46/2332)	1.20	(0.79-1.79)	
OPV campaign or VAS[c] campaign during follow-up							
Observation time split[d] at any OPV+VAS campaign[e]							0.35
Before	16.8	(96/5714)	17.5	(88/5041)	1.01	(0.72-1.42)	
After	11.5	(112/9708)	9.3	(83/8941)	1.24	(0.92-1.68)	
Observation time split[d] at any VAS (± OPV) campaign[f]							0.21
Before	14.7	(51/3479)	16.6	(51/3067)	0.89	(0.59-1.35)	
After	13.1	(157/11944)	11.0	(120/10915)	1.22	(0.93-1.59)	
Observation time split[d] at VAS-only campaign[g]							0.56
Before	14.7	(102/6950)	13.9	(93/6711)	1.04	(0.77-1.42)	
After	12.5	(106/8473)	10.7	(78/7271)	1.20	(0.84-1.73)	

C-MV, Campaign with measles vaccine; MV, measles vaccine; OPV, oral polio vaccine; PYRS, person-years at risk; VAS, vitamin A supplementation.
[a] Adjusted for variables used for the stratified randomization (health region and pre-enrollment vaccination coverage), and sex, and using a robust standard error accounting for intra-cluster correlation. Proportional hazards assumption.
[b] Wald tests to compare effects across strata defined by each potential modifier.
[c] VAS in campaigns was co-administered with mebendazole to children >12 months
[d] Children can contribute with observation time both before the respective campaign and after, unless they experienced an event or had their observation time censored before the respective campaign.
[e] Follow up time split at OPV+VAS campaigns in 2017 (November) or 2018 (April).
[f] Follow up time split at VAS (± OPV) campaigns in 2017 (Jan, Jun, Nov) or 2018 (Apr). To disentangle time since enrollment and VAS campaign effects, we furthermore split follow-up time at 3 months after enrollment. Test of interaction between C-MV, VAS (± OPV) campaigns and timeband (<3 or >3 months from enrollment): $P = 0.95$.
[g] Follow-up time split at VAS-only campaigns in 2017 (January, June). To disentangle time since enrollment and VAS campaign effects, we furthermore split follow-up time at 3 months after enrollment. Test of interaction between C-MV, VAS-only campaign, and time band (<3 or >3 months from enrollment): $P = 0.95$.

selection to enrollment nor differential healthcare-seeking behavior. Nevertheless, the impact of non-blinding is most likely limited by the primary outcome's hard nature and by not disclosing information on group assignments to healthcare providers. Third, because information on deaths/hospital admission was based on parental reports, we cannot rule out imprecision in the date of event or cause of event. For events, we always asked about an event time since the last field visit, which not only enabled us to place the event before or after trial enrollment but also to place it during an approximately 6-month interval. For causes, the most important distinction to be made is between accidental and non-accidental events. Because we expect the accidental nature of an event to be easier to recall than symptoms, we consider parentally reported accident information as valid. Fourthly, whether a potentially changing effect over time is caused by eligibility to health campaigns during follow-up and other concurrent events cannot be disentangled. Finally, we conducted some effect modifier analyses in sub-groups of children, as we only assessed prior vaccinations among children who had their vaccination cards seen at enrollment. Also, some effect modifier analyses were assessed across many strata, such as ethnicity, health region, and different periods of follow-up and calendar time. This combined with our many exploratory analyses should be considered, as it increases the risk of chance findings.

The contrast between our main result and prior studies which found that MV/C-MV reduced the risk of mortality due to other causes than measles [3,5–9] may be explained by several factors. First, the disease burden may have changed. The pre-trial mortality

rate (11.1 intervention/8.9 control) (Table 1) was nearly double the mortality rate observed among the enrolled children (5.3 intervention/4.6 control) (Appendix p 10-11). Thus, we speculate that more recent trials [25–27], including RECAMP-MV, may not be observing beneficial NSEs of MV because the disease pattern has changed. Prior studies have indicated that NSEs of MV are strongest for hospital admissions due to respiratory infections [18,28], where approximately a third were due to respiratory infections [17,18]. However, in RECAMP-MV, only 12% of hospital admissions and 6% of deaths were due to respiratory infections (Appendix p 7). Thus, if the proportion of respiratory infections has declined, then the beneficial NSEs of C-MV could be expected to be smaller. Second, cluster randomization may have created intervention groups and control groups with differential health profiles: The intervention group tended to have higher mortality before RECAMP-MV and more deaths after hospital admission. Third, we had other measures of outcome and exposures. In the studies before RECAMP-MV [5–9], mortality was the main outcome and follow-up time was mostly without exposure to OPV campaigns [5–9]. Furthermore, in some of these studies, C-MV was co-administered with VAS and mebendazole [5,6], which may have interacted with MV [29]. Since the epidemiological review commissioned by the World Health Organization [4], four randomized trials testing NSEs of MV have been conducted [24–27]. Although these four trials did not assess MV implemented as a campaign or among children in the same age group as RECAMP-MV, they did assess the effect of MV on mortality [25–27] or the composite outcome mortality/hospital admission [24] in a similar setting with limited measles. These trials took place during 2011-2019 and randomized children to early MV (at 4.5 months of age) in addition to routine MV (at 9 months of age) [26,27], randomized village clusters to increased MV access regardless of age [25], or randomized children to a 2nd MV dose at 18 months of age [24]. In line with our main result, three of these trials found no overall beneficial effect of MV [25–27] while the fourth trial, which was censored at the time of OPV+VAS campaigns reported a reduction in mortality/hospital admission. Furthermore, despite very sparse events, the trial of increased MV access regardless of age did suggest lower mortality after MV until OPV-only campaigns or OPV+VAS campaigns [25]. Moreover, in a combined analysis of three trials assessing potential beneficial NSEs of early MV, early MV lowered mortality in the absence of OPV+VAS campaigns among children in Guinea-Bissau but tended to increase mortality, particularly for girls, when OPV had been given early in life, although the number of events was small [30].

While our analyses do not allow firm conclusions, we find that the following observations in RECAMP-MV support that OPV+VAS campaigns during follow-up may have interfered with the hypothesized beneficial NSEs of C-MV. First, most RECAMP-MV children had been exposed to OPV+VAS campaigns before enrollment and during follow-up (Table 1). Second, C-MV tended to increase mortality/hospital admission after and not before OPV+VAS campaigns during follow-up (Table 3). Third, as reported elsewhere [20], RECAMP-MV's sub-study suggested that C-MV may have potential beneficial NSEs on outpatient consultations unrelated to measles infection in the short-term; in this sub-group, children were unexposed to OPV+VAS campaigns during follow-up [20], contrary to the total study population in our main result (Table 2). Furthermore, we also explored other potential explanations for the lack of beneficial NSEs of C-MV, but we found no support that the more recently introduced vaccines in the routine vaccination program (Appendix p 16-17), length of follow-up time (Appendix p 20-21), or calendar time (Appendix p 22), explained the lack of beneficial NSEs of C-MV.

In conclusion, the main result did not suggest that a C-MV reduces mortality/hospital admissions, as hypothesized. On the contrary, in the setting of rural Guinea-Bissau, a C-MV tended to have a negative overall health effect. Our exploratory analyses suggested that there is a need to clarify a C-MV's potential interaction with OPV campaigns and/or VAS campaigns, as these interactions may interfere with C-MV's potential beneficial NSEs. However, we cannot rule out other explanations. Some of these explanations may be trial-specific, such as an imbalance in health profiles between intervention and control village clusters, or that changes in infection patterns may have made the NSEs less relevant.

Declarations of competing interest

The authors have no competing interests to declare.

Funding

Real-life Effects of a CAMPaign with Measles Vaccine (RECAMP-MV) would not have been possible without the support of the following funders: Danish National Research Foundation, Fonden af 17-12-1981, University of Southern Denmark, Odense University Hospital, Fabrikant Vilhelm Pedersen og Hustrus legat as per recommendation by Novo Nordisk Fonden, Købmand i Odense Johann og Hanne Weimann, f. Seedorffs Legat, Augustinus Fonden, and Aase og Ejnar Danielsens Fond.

Acknowledgments

We are extremely thankful for everyone who made Real-life Effects of a CAMPaign with Measles Vaccine (RECAMP-MV) possible: mothers/ guardians and their children, regional health directorates, field teams, field supervisors, data entry and data cleaning assistants, management and administration staff, university students, senior researchers (Amabelia Rodrigues, Cesario Martins, and Christine Stabell Benn), data safety and monitoring board members (Morten Frydenberg, Torben Sigsgaard, Anja Poulsen), and internal monitor (Stine Byberg). Finally, we would like to thank Peter Aaby, the founder of Bandim Health Project, for his priceless contributions to conceptualizing RECAMP-MV and critical review of the article.

Author contributions

Authors are mentioned in alphabetical order. ABF oversees Bandim Health Project's rural health and demographic surveillance system platform, designed Real-life Effects of a CAMPaign with Measles Vaccine (RECAMP-MV), drafted the original research protocol, and planned and coordinated RECAMP-MV. ABF, AV, and SMT developed and updated enrollment questionnaires and databases. ABF, AV, LMP, and SMT developed and updated follow-up questionnaires and databases. ABF, AV, LMP, and SMT trained the field teams, supervised the fieldwork, and developed and implemented data cleaning programs. JSDM supervised verbal autopsies and provided diagnoses for hospital admissions and deaths. ABF, AV, AKGJ, and SMT developed the data analysis plans. All authors could access the full data. AV and ABF accessed and verified the data underlying the manuscript. ABF and AV analyzed the data with assistance from AKGJ. AV drafted the manuscript with help from ABF. All authors reviewed and approved the final manuscript.

Data sharing

Deidentified trial data can be made available upon collaborative request. Inquiries can be directed to the senior author at afisker@health.sdu.dk.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.05.011.

References

[1] Orenstein WA, Cairns L, Hinman A, Nkowane B, Olivé JM, Reingold AL. Measles and Rubella Global Strategic Plan 2012–2020 midterm review report: background and summary. *Vaccine* 2018;**36**:A35–42. doi:10.1016/j.vaccine.2017.10.065.

[2] United Nations Inter-agency Group for Child Mortality Estimation *Levels and trends in child mortality [report]*. New York: UNICEF; 2019.

[3] Benn CS, Fisker AB, Rieckmann A, Sørup S, Aaby P. Vaccinology: time to change the paradigm? *Lancet Infect Dis* 2020;**20**:e274–83. doi:10.1016/S1473-3099(19)30742-X.

[4] Higgins JP, Soares-Weiser K, López-López JA, Kakourou A, Chaplin K, Christensen H, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ* 2016;**355**:i5170. doi:10.1136/bmj.i5170.

[5] Byberg S, Thysen SM, Rodrigues A, Martins C, Cabral C, Careme M, et al. A general measles vaccination campaign in urban Guinea-Bissau: comparing child mortality among participants and non-participants. *Vaccine* 2017;**35**:33–9. doi:10.1016/j.vaccine.2016.11.049.

[6] Fisker AB, Rodrigues A, Martins C, Ravn H, Byberg S, Thysen S, et al. Reduced all-cause child mortality after general measles vaccination campaign in rural Guinea-Bissau. *Pediatr Infect Dis J* 2015;**34**:1369–76. doi:10.1097/INF.0000000000000896.

[7] Koenig MA, Khan MA, Wojtyniak B, Clemens JD, Chakraborty J, Fauveau V, et al. Impact of measles vaccination on childhood mortality in rural Bangladesh. *Bull World Health Organ* 1990;**68**:441–7.

[8] Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and reduction in child mortality: a community study from Guinea-Bissau. *J Infect* 1984;**8**:13–21. doi:10.1016/s0163-4453(84)93192-x.

[9] Aaby P, Whittle H, Benn CS. Vaccine programmes must consider their effect on general resistance. *BMJ* 2012;**344**:e3769. doi:10.1136/bmj.e3769.

[10] Varma A, Jensen AKG, Thysen SM, Pedersen LM, Aaby P, Fisker AB. Research protocol of two concurrent cluster-randomized trials: Real-life Effect of a CAMPaign with Measles Vaccination (RECAMP-MV) and Real-life Effect of a CAMPaign with Oral Polio Vaccination (RECAMP-OPV) on mortality and morbidity among children in rural Guinea-Bissau. *BMC Public Health* 2019;**19**:1506. doi:10.1186/s12889-019-7813-y.

[11] World Health Organisation. Measles reported cases and incidence, https://immunizationdata.who.int/pages/incidence/MEASLES.html?CODE=GNB&YEAR=; 2022 [accessed 11 March 2023].

[12] World Health Organisation. Measles vaccination coverage, https://immunizationdata.who.int/pages/coverage/mcv.html?CODE=GNB&ANTIGEN=MCV1&YEAR=; 2022 [accessed 11 March 2023].

[13] Loevinsohn B, Hong R, Gauri V. Will more inputs improve the delivery of health services? Analysis of district vaccination coverage in Pakistan. *Int J Health Plann Manage* 2006;**21**:45–54. doi:10.1002/hpm.824.

[14] Thysen SM, Fernandes M, Benn CS, Aaby P, Fisker AB. Cohort profile: Bandim Health Project's (BHP) rural Health and Demographic Surveillance System (HDSS)-a nationally representative HDSS in Guinea-Bissau. *BMJ Open* 2019;**9**:e028775. doi:10.1136/bmjopen-2018-028775.

[15] INDEPTH network. Indepth verbal autopsy, http://www.indepth-network.org/index.php?option=com_content&task=view&id=96&Itemid=184; 2023 [accessed 04 April 2017].

[16] World Health Organisation. Summary of measles-rubella supplementary immunization activities, https://immunizationdata.who.int/listing.html?topic=&location=GNB; 2023 [accessed 25 March 2023].

[17] Brønd M, Martins CL, Byberg S, Benn CS, Whittle H, Garly ML, et al. Randomized trial of 2 versus 1 dose of measles vaccine: effect on hospital admission of children after 9 months of age. *J Pediatric Infect Dis Soc* 2018;**7**:226–33. doi:10.1093/jpids/pix042.

[18] Martins CL, Benn CS, Andersen A, Balé C, Schaltz-Buchholzer F, Do VA, et al. A randomized trial of a standard dose of Edmonston-Zagreb measles vaccine given at 4.5 months of age: effect on total hospital admissions. *J Infect Dis* 2014;**209**:1731–8. doi:10.1093/infdis/jit804.

[19] Nielsen BU, Byberg S, Aaby P, Rodrigues A, Benn CS, Fisker AB. Seasonal variation in child mortality in rural Guinea-Bissau. *Trop Med Int Health* 2017;**22**:846–56. doi:10.1111/tmi.12889.

[20] Varma A, Aaby P, Thysen SM, Jensen AKG, Fisker AB. Reduction in short-term outpatient consultations after a campaign with measles vaccine in children aged 9–59 months: substudy within a cluster-randomized trial. *J Pediatric Infect Dis Soc* 2020;**9**:535–43. doi:10.1093/jpids/piaa091.

[21] Benn CS, Fisker AB, Whittle HC, Aaby P. Revaccination with live attenuated vaccines confer additional beneficial nonspecific effects on overall survival: a review. *EBiomedicine* 2016;**10**:312–17. doi:10.1016/j.ebiom.2016.07.016.

[22] Aaby P, Andersen A, Martins CL, Fisker AB, Rodrigues A, Whittle HC, et al. Does oral polio vaccine have non-specific effects on all-cause mortality? Natural experiments within a randomised controlled trial of early measles vaccine. *BMJ Open* 2016;**6**:e013335. doi:10.1136/bmjopen-2016-013335.

[23] Benn CS, Aaby P, Arts RJ, Jensen KJ, Netea MG, Fisker AB. An enigma: why vitamin A supplementation does not always reduce mortality even though vitamin A deficiency is associated with increased mortality. *Int J Epidemiol* 2015;**44**:906–18. doi:10.1093/ije/dyv117.

[24] Berendsen MLT, Silva I, Balé C, Nielsen S, Hvidt S, Martins CL, et al. The effect of a second dose of measles vaccine at 18 months of age on nonaccidental deaths and hospital admissions in Guinea-Bissau: interim analysis of a randomized controlled trial. *Clin Infect Dis* 2022;**75**:1370–8. doi:10.1093/cid/ciac155.

[25] Byberg S, Aaby P, Rodrigues A, Stabell Benn C, Fisker AB. The mortality effects of disregarding the strategy to save doses of measles vaccine: a cluster-randomised trial in Guinea-Bissau. *BMJ Glob Health* 2021;**6**. doi:10.1136/bmjgh-2020-004328.

[26] Fisker AB, Nebie E, Schoeps A, Martins C, Rodrigues A, Zakane A, et al. A two-center randomized trial of an additional early dose of measles vaccine: effects on mortality and measles antibody levels. *Clin Infect Dis* 2018;**66**:1573–80. doi:10.1093/cid/cix1033.

[27] Nielsen S, Fisker AB, da Silva I, Byberg S, Biering-Sørensen S, Balé C, et al. Effect of early two-dose measles vaccination on childhood mortality and modification by maternal measles antibody in Guinea-Bissau, West Africa: a single-centre open-label randomised controlled trial. *EClinicalmedicine* 2022;**49**:101467. doi:10.1016/j.eclinm.2022.101467.

[28] Nielsen S. *PhD thesis: The eradication paradox: can stopping oral polio vaccine have negative consequences?* University of southern Denmark; 2022.

[29] Fisker AB, Bale C, Rodrigues A, Balde I, Fernandes M, Jørgensen MJ, et al. High-dose vitamin A with vaccination after 6 months of age: a randomized trial. *Pediatrics* 2014;**134**:e739–48. doi:10.1542/peds.2014-0550.

[30] Sørup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. *JAMA* 2014;**311**:826–35. doi:10.1001/jama.2014.470.